Abstract: Tularemia as a Biological Weapon: Medical and Public Health Management

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A working group of 25 representatives from major academic medical centers and research, government, military, public health and emergency management institutions and agencies developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of tularemia as a biological weapon against a civilian population. Their consensus recommendations covered the following seven areas:

1. Pathogenesis and clinical manifestations
2. Diagnosis
3. Vaccination
4. Treatment
5. Postexposure prophylaxis
6. Infection control and environmental decontamination
7. Additional research needs

Background

- Tularemia, a bacterial zoonosis, is caused by *Francisella tularensis*, one of the most infectious pathogenic bacteria known. It requires inoculation or inhalation of as few as 10 organisms to cause disease.
- *F. tularensis* is a small, nonmotile, aerobic, gram-negative coccobacillus. It has a thin lipopolysaccharide-containing envelope and is a hard, non-spore-forming organism that survives for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses.
- Tularemia occurs throughout much of North America and Eurasia. In the U.S., human cases have been reported from every state except Hawaii, with the majority occurring in south-central and western states.
- *F. tularensis* is found in widely diverse animal hosts and habitats and can be recovered from contaminated water, soil, and vegetation. A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares are natural reservoirs of infection. They acquire infection through tick, fly, and mosquito bites and by contact with contaminated environments. Epizootics with sometimes extensive die-offs of animal hosts may herald outbreaks of tularemia in humans.
- Humans can become incidentally infected through diverse environmental exposures: bites by infected arthropods; handling infectious animal tissues or fluids; direct contact with or ingestion of contaminated food, water, or soil; and inhalation of infective aerosols. Humans can develop severe and sometimes fatal illness, but do not transmit the disease to others.
- Worldwide incidence of naturally occurring tularemia is unknown. It is likely that the disease is greatly under-recognized and under-reported. In the U.S., reported cases have dropped sharply from several thousand/year prior to 1950 to fewer than 200/year in the 1990s. Between 1985 and 1992, 1409 cases and 20 deaths were reported in the U.S., a case fatality rate of 1.4%. Most U.S. cases occur June–September, when arthropod-borne transmission is

most common. Cases in winter most commonly occur among hunters and trappers who handle infected animal carcasses.

- *F. tularensis* could be used as a biological weapon in a number of ways, but an aerosol release would likely have the greatest adverse medical and public health consequences.
- Airborne *F. tularensis* would be expected to principally cause pleuropneumonitis, but some exposures might contaminate the eye, resulting in ocular tularemia; penetrate broken skin, resulting in ulceroglandular or glandular disease; or cause oropharyngeal disease with cervical lymphadenitis.
- Release in a densely populated area would be expected to result in an abrupt onset of large numbers of acute, nonspecific febrile illness beginning 3–5 days later (incubation range 1–14 days), with pleuropneumonitis developing in a significant proportion of cases during the ensuing days and weeks.

1. Pathogenesis and clinical manifestations of tularemia

- *F. tularensis* can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. It is a facultative intracellular bacterium that multiplies within macrophages. The major target organs are the lymph nodes, lungs and pleura, spleen, liver, and kidney. Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to regional lymph nodes and further multiply, and then may disseminate to organs throughout the body.
- Bacteremia may be common in the early phase of infection. The initial tissue reaction to infection is a focal, intensely suppurative necrosis consisting largely of accumulations of polymorphonuclear leukocytes, followed by invasion of macrophages, epithelioid cells, and lymphocytes.
- Suppurative lesions become granulomatous, and histopathological examination of the granulomas shows a central necrotic, sometimes caseating, zone surrounded by a layer of epithelioid cells, multinucleated giant cells, and fibroblasts in a radial arrangement, typical of other granulomatous conditions such as tuberculosis and sarcoidosis.
- Humans with inhalational exposures also develop hemorrhagic inflammation of the airways early in the course of illness, which may progress to bronchopneumonia. Histopathological examination of the lungs shows alveolar spaces filled with an exudate of mononuclear cells. Pleuritis with adhesions and effusion and hilar lymphadenopathy are common in radiological and pathological findings.
- Primary clinical forms vary in severity and presentation according to virulence of the infecting organism, dose, and site of inoculum.
- The onset of tularemia is usually abrupt, with fever (38°C–40°C), headache, chills and rigors, generalized body aches (often prominent in the low back), coryza, and sore throat. A pulse-temperature dissociation has been noted in as many as 42% of patients. A dry or slightly productive cough and substernal pain or tightness frequently occur with or without objective signs of pneumonia, such as purulent sputum, dyspnea, tachypnea, pleuritic pain, or hemoptysis. Nausea, vomiting, and diarrhea may occur.
- Sweats, fever, chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness.
- In general, tularemia would be expected to have a slower progression of illness and a lower case-fatality rate than either inhalational plague or anthrax. Milder forms of inhalational tularemia would be indistinguishable from Q fever; another potential bioterrorism agent; establishing a diagnosis of either would be problematic without reference laboratory testing.

2. Diagnosis

- Rapid diagnostic testing for tularemia is not widely available. Physicians who suspect inhalational tularemia in patients presenting with atypical pneumonia, pleuritis, and hilar lymphadenopathy should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures.
- *F. tularensis* may be identified through direct examination of secretions, exudates, or biopsy specimens using Gram stain, direct fluorescent antibody, or immunohistochemical stains. Microscopic demonstration of *F. tularensis* using fluorescent-labeled antibodies is a rapid diagnostic procedure performed in designated reference laboratories in the National Public Health Laboratory Network; test results can be available within several hours of receiving the specimens, if the laboratory is alerted and prepared.
- Growth of *F. tularensis* in culture is the definitive means of confirming the diagnosis of tularemia. It can be grown from pharyngeal washings, sputum specimens, and even fasting gastric aspirates in a high proportion of patients with inhalational tularemia. It is only occasionally isolated from blood.

3. Vaccination

- In the United States, a live attenuated vaccine derived from avirulent *F. tularensis* biovar palaearctica (type B) has been used to protect laboratorians routinely working with the bacterium. Until recently, this vaccine was available as an investigational new drug. It is currently under review by the Food and Drug Administration.

4. Treatment

- In a contained casualty setting, where individual patient management is possible, the working group recommends parenteral antimicrobial therapy. Streptomycin is the drug of choice. Gentamicin, which is more widely available and can be used intravenously, is an acceptable alternative. Treatment with aminoglycosides should be continued for 10 days. Tetracyclines and chloramphenicol are also used, but relapses and primary treatment failures occur at a higher rate with these bacteriostatic agents than with aminogylcosides, and they should be given for at least 14 days to avoid relapse. Both streptomycin and gentamicin are recommended as first-line treatment of tularemia in children.
- In a mass casualty setting, doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment of both adults and children.
- Since it is unknown whether drug-resistant organisms might be used in a bioterrorist event, antimicrobial susceptibility testing of isolates should be conducted quickly and treatments altered according to test results and clinical responses.
- Antibiotics for treating patients infected with tularemia in a bioterrorist event are included in the national pharmaceutical stockpile maintained by CDC, as are ventilators and other emergency equipment.

Working Group Consensus Recommendations for Treatment of Patients With Tularemia in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis*

Patient Category	Recommended Therapy
Contained Casualty	
Adults	**Preferred choices:** Streptomycin, 1g IM twice daily Gentamicin, 5 mg/kg IM or IV once daily† **Alternative choices:** Doxycycline, 100 mg IV twice daily Chloramphenicol, 15 mg/kg IV 4 times daily Ciprofloxacin, 400 mg IV twice daily†
Children	**Preferred choices:** Streptomycin, 15 mg/kg IM twice daily (should not exceed 2 gm/d) Gentamicin, 2.5 mg/kg IM or IV 3 times daily† **Alternative choices:** Doxycycline, If weight>= 45 kg, 100 mg IV If weight < 45 kg, give 2.2 mg/kg IV twice daily Chloramphenicol, 15 mg/kg IV 4 times daily† Ciprofloxacin, 15 mg/kg IV twice daily‡
Pregnant Women	**Preferred choice:** Gentamicin, 5 mg/kg IM or IV once daily† Streptomycin, 1 g IM twice daily **Alternative choices:** Doxycycline, 100 mg IV twice daily Ciprofloxacin, 400 mg IV twice daily†
Mass Casualty Setting and Postexposure Prophylaxis	

Adults	**Preferred choices:** Doxycycline, 100 mg orally twice daily Ciprofloxacin, 500 mg orally twice daily†
Children	**Preferred choices:** Doxycycline, and If >=45kg give 100 mg orally twice daily If <45 kg then give 2.2 mg/kg orally twice daily Ciprofloxacin, 15 mg/kg orally twice daily‡
Pregnant Women	**Preferred choices:** Ciprofloxacin, 500 mg orally twice daily† Doxycycline, 100 mg orally twice daily

* One antibiotic, appropriate for treatment for patient age, should be chosen from among the alternatives. Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14-21 days. Persons beginning treatment with intramuscular (IM) or intravenous (IV) doxycycline, ciprofloxacin, or chloramphenicol can switch to oral antibiotic administration when clinically indicated.

† Not a U.S. Food and Drug Administration-approved use.

‡ Ciprofloxacin dosage should not exceed 1 g/d in children.

5. Postexposure prophylaxis

- Persons beginning treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin in the incubation period of tularemia and continuing treatment daily for 14 days might be protected against symptomatic infection. Therefore, if an attack is discovered before individuals become ill, exposed persons should be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin.
- If an attack is discovered only after individuals become ill, persons potentially exposed should begin a fever watch. Those who develop an otherwise unexplained fever or flu-like illness within 14 days of presumed exposure should begin treatment as outlined above.
- Postexposure prophylactic treatment of close contacts of tularemia patients is not recommended because person-to-person transmission is not known to occur.

6. Infection control and environmental decontamination

- Isolation is not recommended for tularemia patients, given the lack of person-to-person transmission. In hospitals, standard precautions are recommended.
- Laboratory personnel should be alerted when tularemia is suspected. Routine diagnostic procedures can be performed in biosafety level 2 conditions. Examination of cultures in which *F. tularensis* is suspected should be done in a biological safety cabinet. Manipulation of cultures and other procedures that might produce aerosols or droplets (e.g., grinding,

centrifuging, vigorous shaking, animal studies) should be conducted under biosafety level 3 conditions.

- Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to produce aerosols or droplets should be avoided.
- Clothing or linens contaminated with body fluids of patients with tularemia should be disinfected per standard hospital procedure.
- Under natural conditions, *F. tularensis* can survive for extended periods in a cold, moist environment. Information is not available about survivability of an intentionally released aerosol form of *F. tularensis*, but the working group predicts a short half-life due to desiccation, solar radiation, oxidation, and other environmental factors and a very limited risk from secondary dispersal. Following an urban release, the risk to humans of acquiring tularemia from infected animals or arthropods is likely small and can be reduced by educating the public to avoid sick or dead animals and to take precautions to protect against biting arthropods.

7. Additional research needs

- Simple, rapid, and reliable diagnostic tests to identify infected patients need to be developed. Likewise, tests are needed to detect *F. tularensis* in environmental samples.
- Additional genetic information is needed to understand genetic variants, functions of genes and mechanisms of action useful against *F. tularensis*.
- Vaccines for pre- or postexposure protection are needed.